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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,461	12/11/2003	Michael P. Czech	UMY-055RCE	3119

959 7590 06/19/2008

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,461	CZECH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 38-86* is/are pending in the application.

4a) Of the above claim(s) *60-78 and 80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,38-59,79 and 81-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A response was received and entered on 4/3/08.

Claims 60-78 and 80 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/22/06.

Claims 27, 38-59, 79, and 81-86 are under consideration in this Action. Claim 81 is considered only to the extent that it depends from claim 79.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27, 38-48, 50, 51, 56-59, 79, and 81-86 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) in view of Clancy et al (US 20030087259) and Paquereau et al (Anal. Biochem. 204(1): 147-151, 1992).

Al Hasani taught methods of studying genes related to glucose transport. Specifically, Al-Hasani investigated the relationship between the GTPase dynamin and insulin-stimulated endocytosis of the GLUT4 glucose transporter in cultured primary rat adipocytes. Adipocytes were transfected by electroporation with a construct for

expressing an easily detectable (HA)-tagged GLUT4, and then with constructs for over-expression of either wild type dynamin or a GTPase-negative mutant of dynamin. Electroporation voltage was 0.2 kV. The effects of these dynamins on (HA)-tagged GLUT4 endocytosis after insulin treatment was measured. Al-Hasani showed that endocytosis of GLUT4 is largely mediated by processes that require dynamin. See abstract, paragraph bridging pages 17505 and 17506, Fig. 2 on page 17506, and Fig. 3 on page 17507.

Al Hasani did not teach the use of siRNA to achieve inhibition of dynamin activity, and was silent as to the capacitance setting for use in electroporation

Clancy taught that the activity of a polypeptide in a cell can be controlled by several alternative means including the use of negative mutants of the protein and the use of antisense or siRNA directed at the mRNA encoding the protein. See summary of invention paragraph 9, detailed description paragraph 234, and claim 21.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use siRNA directed against dynamin to assess its role in the endocytosis of GLUT4. For example, one could have used anti-dynamin siRNA to down-regulate wild type dynamin activity instead using the negative dynamin mutant. This experiment would result in down regulation of the endogenous dynamin (as required by instant claim 59) and the exogenous dynamin expressed from the expression construct (as required by instant claim 58). Further, one of ordinary skill in the art appreciates that the effects of the negative dynamin mutant could be confirmed by reversing them through the use of siRNA directed against the mutant. It would have been obvious to

deliver the siRNA by electroporation because Al-Hasani demonstrated that this method was suitable for delivering nucleic acids to adipocytes. However, these references were silent as to the capacitance used for electroporation.

Paquereau taught a method of delivering nucleic acids to mammalian cells by electroporation using a potential of 0.15-0.2 kV and a capacitance of 960 micro F. These conditions minimized cell damage and increased cell survival. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the electrical potential and capacitance used in the electroporation of the cells of Al-Hasani because it was recognized in the art that these variables could affect the amount of cell damage caused by electroporation, as well as cellular survival after electroporation. In so doing, one of ordinary skill would have noted that Al-Hasani used a voltage in the range used by Paquereau, and so would have been motivated to use a capacitance in the range used by Paquereau with the reasonable expectation of obtaining minimal cellular damage and improved cellular survival. Note that Paquereau used the exact capacitance required by instant claim 43.

Regarding claims 44-46, the temperature of electroporation, and the time between electroporation and assay, are considered to be variables that are routinely optimized by those of ordinary skill in the art, and so are considered to be obvious.

Claims 53-55 are included in the rejection because these claims, which require increased siRNA stability, or increased or decreased siRNA activity, recite no standard against which to compare stability or activity. One of ordinary skill in the art possesses the ability to modify a given siRNA to have greater or lesser activity and stability by

incorporation of a greater or lesser number of modified bases. So, any given siRNA has greater or lesser activity than a differently modified one. In the absence of any standard of comparison these limitations carry no weight.

Claim 56 is included in the rejection because those of ordinary skill in the art appreciate that glucose metabolism is important in a variety of human diseases including diabetes. As a result it would be obvious to perform similar experiments in human cells.

Regarding claims 82 and 83, the concentrations of cells and siRNAs in the electroporation mixture are considered to be result-effective variables that are routinely optimized by those of ordinary skill in the art. Note that Al Hasani electroporated 200 microliters of cells at a concentration of 5-6 $X10^6$ cells per ml, i.e. about 1 million cells.

Claim 49 stands rejected under 35 U.S.C. 103(a) as being unpatentable Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) in view of Clancy et al (US 20030087259) and Paquereau et al (Anal. Biochem. 204(1): 147-151, 1992), as applied to claims 27, 38-48, 50, 51, 56-59, 79, and 81-86 above, and further in view of Standaert et al (J. Biol. Chem. 272(48): 30075-30082, 1997).

The teachings of Al-Hasani, Clancy, and Paquereau are summarized above and can be combined to render obvious methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation at 0.15-0.2 kV and 960 microFarads.

The references do not teach an assay of glucose uptake.

Standaert taught method of studying the effect of a gene expression of protein kinase C zeta (PKC-zeta) on glucose transport. Assays included measurement of GLUT4 translocation as well as glucose uptake. See abstract, paragraphs bridging pages 30078 to 30080, and Figs 7 and 8 on page 30079.

It would have been obvious to one of ordinary skill in the art at the time of the invention to extend the studies of Al-Hasani to studies of glucose uptake. One of ordinary skill in the art, interested in the effects of genes on glucose transport, would have realized that GLUT4 translocation and GLUT4 transport activity can both be used as measures of the effect of a gene product on glucose transport, and would have been motivated to use either one. However, one would have been particularly motivated to assay glucose uptake directly given that is the actual function of GLUT4, and so would provide a more accurate representation of the effects of the gene product on glucose transport.

Claims 52-55 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) in view of Clancy et al (US 20030087259) and Paquereau et al (Anal. Biochem. 204(1): 147-151, 1992), as applied to claims 27, 38-48, 50, 51, 56-59, 79, and 81-86 above, and further in view of McSwiggen et al (US Patent 7,022,828).

The teachings of Al-Hasani, Clancy, and Paquereau are summarized above and can be combined to render obvious methods of identifying a gene that affects glucose

transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation at 0.15-0.2 kV and 960 microFarads.

The references do not teach siRNA derivatives.

McSwiggen taught methods of inhibiting gene expression using siRNA, and taught that the stability of siRNA molecules could be enhanced through the use of modified bases. See and column 25, lines 58-67 claim 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use modified siRNA oligonucleotides in the invention of Al-Hasani as modified by Clancy and Paquereau. One would have been motivated to do so in order to enhance the function of the oligonucleotides, as taught by McSwiggen.

Response to Arguments

Applicant's arguments filed 4/3/08 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 11-22 of the response. Applicant reiterates arguments that one of skill would have found neither a reasonable expectation of success, nor the motivation to arrive at the claimed invention. These arguments are unpersuasive for the reasons of record. It was clear to those of ordinary skill in the art at the time of the invention that adipocytes could be transfected by electroporation, it was routine in the art at that time to optimize electroporation conditions, and the conditions used by Applicant to obtain siRNA delivery were

conditions that were routinely used in the prior art for the delivery of nucleic acids to mammalian cells (see Al-Hasani and Paquereau above).

Applicant that the claims are non-obvious because they require expression of the target gene to be reduced by at least 70% in the culture of adipocytes. This is unpersuasive. It is important to note that the limitation "expression of the target gene is reduced by at least 70% in the culture of adipocytes" in no way limits the fraction or number of adipocytes in the culture in which expression of the target gene is reduced. Thus 70% reduction of target gene expression in a only a single cell in the culture would meet this limitation. Applicant has presented no evidence that this would not occur using the method of Al-Hasani as modified by Clancy and Paquereau. As pointed out previously, Al-Hasani achieved up to 10% transfection efficiency when electroporating rat primary adipocytes using a voltage (0.2kV) in the center of the range claimed by Applicant. It is well accepted in the art, and apparent from the teachings of Paquereau (1992), Weil (2002, cited previously by Applicant) and Walters (2002, cited previously by Applicant) that the conditions of electroporation of mammalian cells were result effective variables that were obvious to optimize at the time of the invention. Further, Paquereau combined a voltage in the range of 0.15 to 0.2 kV and a capacitance of 960 microFarads for electroporating mammalian cells, the exact conditions used by Applicant to achieve 70% reduction in expression. So, it is clear that the values of voltage and capacitance used by Applicant to achieve electroporation were routinely used by those of ordinary skill prior to the invention for the purpose of electroporating nucleic acids into mammalian cells. One of ordinary skill seeking to electroporate

siRNA into adipocytes would reasonably have started with the voltage that Al-Hasani used for adipocytes, and then optimized the capacitance. In view of the teachings of Paquereau, 960 microFarads was routinely used in the transfection of mammalian cells. So one of ordinary skill could easily have arrived at the instantly claimed electroporation conditions through routine optimization.

Applicant argues at page 12 that it is essential to the invention that the adipocyte population exhibit sufficient reduction in expression of the targeted gene to be able to reliably assay that gene's effect on glucose transport. Applicant indicates at page 13 that the methodology of Al-Hasani is designed to transfect adipose cells with DNA and DNA expression plasmids, including 5 micrograms of plasmid and 100 micrograms of carrier DNA. Applicant states that it would not have been obvious, based on the teachings of Al-Hasani, who achieved only up to 10% transfection efficiency, that successful electroporation of an adipocyte population with siRNA such that gene reduction would occur at a level suitable to assay the genes effect on the glucose transport activity of the adipocyte population could be accomplished. This is unpersuasive for the reasons of record. Al Hasani was capable of studying the effect on GLUT4 intracellular recycling by recombinant expression of GLUT4 and either GTPase dynamin or a GTPase-negative dynamin when achieving only 10% transfection efficiency. Applicant has not explained why any greater level of transfection efficiency would be required for obtaining siRNA function. As mentioned above, the claims do not require that target gene expression is reduced by 70% in the culture as a whole, the claims require this level of reduction in only a single cell of the population. Applicant

has presented no evidence that the method of Al-Hasani as modified by Clancy and Paquereau would not function to deliver sufficient siRNA to achieve this level of inhibition in at least one cell.

At page 14 Applicant reiterates arguments that siRNAs and DNAs are quite different chemical entities, such that one of ordinary skill would have had no reasonable expectation of success in utilizing certain parameters disclosed in Paquereau for transfection of large amounts of DNA to arrive at the claimed siRNA electroporation methods. This is unpersuasive for the reasons of record. Actually, siRNAs and DNAs are quite similar chemical entities inasmuch as they are both double stranded nucleic acids and have identical charge densities. The teachings of Weil (2002) make clear that establishing siRNA electroporation conditions was a matter of routine optimization and that electroporation "can, a priori, be adapted to all cell types". Weil suggested that electroporation of siRNAs can be efficient for nonadherent cells, and indicated that the optimal parameters for the electroporation of siRNA differ from those of plasmids, allowing the use of milder conditions that induce less cell toxicity. See abstract. Note also that in optimizing the electroporation parameters on mammalian cells, Weil used the combinations of 0.3 kV/ 125 microFarads; 0.28 kV /250 microFarads; and 0.26 kV/960 microFarad (see page 1245, column 1, last paragraph). Only claims 41-43 recite a parameter not anticipated by Weil. The instant claims recite capacitance in the range examined by Weil, but have voltages slightly outside the range of Weil. However, in view of the range of voltages embraced by the claims, one of ordinary skill would be led to believe that the voltage parameter is not critical outside a range of 0.01 kV to 2.0

kV when using capacitance of 960 microFarads. Accordingly, Weil only provides further evidence of the obviousness of each of the instant claims.

Walters (2002) used electroporation to delivery siRNA to human cells to circumvent problems associated with the uptake through the endosome/lysosome pathway because it was known in the prior art that electroporation allowed direct delivery to the cytosol and did not depend on the endosome/lysosome (endocytic) pathway. This provides evidence that it was routine in the art at the time of the invention to optimize transfection protocols to determine which protocol worked best for a given cell line. In view of the teachings of Weil and Walter, as well as the structural similarity of dsRNA and dsDNA, one of ordinary skill could clearly have optimized DNA electroporation parameters to effectively deliver siRNA through routine experimentation.

At page 14, Applicant argues that there is no motivation to select siRNAs from the list of gene function inhibitors disclosed by Clancy. This is unpersuasive. In view of the teachings of Clancy, it was clear that the prior art recognized a variety of means to inhibit gene function. These means can be viewed as equivalent alternatives for achieving the same result, i.e. inhibition of gene function. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious.

At the paragraph bridging pages 14 and 15, Applicant alleges that the Office Action failed to provide any reason to combine the cited references. This is incorrect.

With regard to the combination of Clancy with Al-Hasani, negative mutants and siRNAs are considered to be exchangeable alternative tools for inhibiting gene function in view of the teachings of Clancy. Further, as stated in the rejection, use of anti-dynamin siRNA to down-regulate wild type dynamin would result in down regulation of the endogenous dynamin (as required by instant claim 59) and the exogenous dynamin expressed from the expression construct (as required by instant claim 58). Further, one of ordinary skill in the art appreciates that the effects of the negative dynamin mutant could be confirmed by reversing them through the use of siRNA directed against the mutant. With regard to the addition of Paquereau, this reference provides evidence that the voltage and capacitance recited in the instant claims were known to be used for mammalian cells. Al-Hasani already taught the recited voltage, but was silent as to the capacitance. As stated in the rejection, one of ordinary skill appreciates that voltage and capacitance are result-effective variables (see Paquereau, abstract), and it is obvious to optimize such variables. Because Al-Hasani taught a voltage that functioned to electroporate adipocytes but did not disclose capacitance, one of ordinary skill would have been motivated to use Al-Hasani's voltage and then optimize the capacitance. See above.

At pages 15-17 Applicant discusses the relevance of unexpected results and skepticism of experts. In this section, Applicant reiterates the unsupported allegation that in order to successfully silence a gene of interest in a population of adipocytes it is required that virtually all of the cultured adipocytes take up the siRNA. This is false. The claims do not require any particular threshold level of transfection efficiency.

Furthermore, as state previously and above, Al Hasani managed to identify a gene that affects glucose uptake by transfecting an inhibitory nucleic acid into no more than 10% of an adipocyte population. Applicant has not explained why 100% transfection efficiency would be required when studying glucose transport using siRNA to downregulate a cellular process, when 10% efficiency (or far less) was sufficient for studying the same process by transfection of separate expression vectors encoding GLUT4 and dynamin.

Applicant relies upon this unsupported allegation of a requirement of 100% efficiency to support an argument that one of ordinary skill would not have reasonably expected the combined references to provide adequate transfection efficiency to practice the method. The argument is unpersuasive because its basis is unsupported for the reasons in the previous paragraph. In any event, the unexpected results were obtained using specific electroporation conditions that are recited only in claim 43, so only claim 43 could be considered to be commensurate in scope with the unexpected results. Accordingly, even if Applicant's arguments regarding unexpected results were persuasive, which they are not, they could only be persuasive with regard to claim 43.

Applicant argues that the art is replete with teachings indicating that adipocytes are recognized as difficult to transfect relying on the Jain and Venugopal references. Applicant also cites Robinson as indicating that adipocytes are difficult to transfect, and note that Robinson cites a paper authored by instant inventor Czech as being the first demonstration of transfection of adipocytes with siRNA using electroporation. The Examiner agrees that it was recognized in the prior and post-filing art that it was difficult

to transfect adipocytes. However this does not change the fact that it was known that adipocytes could be transfected by electroporation, the fact that transfection electroporation conditions were routinely optimized, or the fact that the precise conditions used by Applicant were applied to other mammalian cells in the prior art. Accordingly it would have been obvious to one of ordinary skill in the art to arrive at the claimed electroporation conditions in the course of routine optimization, particularly in view of the fact that the voltage used by Applicant had been used with success on adipocytes in the prior art. Applicant's discussion of the Walters (2002) and Weil (2002) references was addressed in the previous action and above. These references provide further support for the position that it is obvious to optimize electroporation voltage and capacitance when performing electroporation as discussed above.

At pages 17 and 18, Applicant presents an analysis of copying and commercial success as it may be relevant to obviousness. Applicant cites Robinson and the Panomics Deliver X brochure as indicating that adipocytes are difficult to transfect, and as noting that the instant inventors provided the first demonstration of transfection of adipocytes with siRNA using electroporation. The Examiner concedes that Applicant was the first to transfect adipocytes with siRNA, and that transfection of adipocytes was known to be difficult. However, when viewing the record as a whole, it was clear that adipocytes could be electroporated with nucleic acids, it was clear that it was obvious to optimize electroporation voltage and capacitance, the instantly claimed voltages had been used to electroporate adipocytes previously, the voltage and capacitance which gave the best results had been used on several different cell types in the prior art (see

Paquereau, abstract, and Weil at paragraph bridging columns 1 and 2 on page 1245), and it was clearly obvious to use siRNA to manipulate gene expression. Based on an analysis of the record as a whole, the claimed invention would have been obvious to one of ordinary skill at the time of the invention.

At pages 18-23, Applicant provides a response to the non-final action of 10/3/2007. At page 19, Applicant addresses the statement that "Applicant has not explained why 100% transfection efficiency would be required…". Applicant argues that the invention is a novel methodology capable of silencing gene expression in virtually every adipocyte in a population, and that this key aspect of the invention is featured in the claims. This is unpersuasive precisely because Applicant is arguing limitations that are not in the claims. No claim recites any limitation regarding transfection efficiency. Furthermore, in light of Applicant's arguments regarding unexpected results, any claim that did require transfection of virtually every adipocyte in a population would seem to also require limitations on the capacitance and voltage required to produce such results.

Applicant's arguments at pages 20-23 are unpersuasive for the reasons set forth above and in previous actions. For these reasons the rejections are maintained.

References Made of Record But Not Relied Upon

US Patents 5459058, 5565321, 5624803, 5674500, 5744327, 5767077, 5804380, 5834266, 5882914, 6265160, 6274708, 6340577, 6365369, 6372173, 6495581, 6576664, 6642041, 6756355, 6855808, 6921665, 7034134, and 7223791

each teach nucleic acid delivery to mammalian cells by electroporation using a capacitance of 960 micro Farads and a potential in the range of 180-300V. Each of these references antedates the instant application.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635